

## REMARKS

In response to the above-identified Office Action (“Action”), Applicants traverse the Examiner’s rejection of the claims and seek reconsideration thereof. Claims 38, 42-57 and 60-67 are pending in the present application. Claims 38, 42-57 and 60-67 are rejected. In this response, claims 38 and 57 are amended, claim 67 is cancelled and no claims are added.

### **I. Claim Amendments**

Applicants respectfully submit the amendments do not add new matter and are supported by the specification. Accordingly, Applicants respectfully request reconsideration and entry of the amendments to claims 38 and 57.

### **II. Claim Rejections – 35 U.S.C. §103**

A. In the Action, claims 38, 42-57, and 60-67 are rejected under 35 U.S.C. §103(a) as being unpatentable over International Publication No. WO 95/02069 issued to Bennett et al. (“Bennett”), in view of Journal of Biological Chemistry, 1993, Vol. 268:16:11742-11749 of Park et al. (“Park”).

To establish a *prima facie* case of obviousness, the Examiner must set forth “some articulated reasoning with some rational underpinning to support the conclusion of obviousness.” See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2007). In combining prior art elements to render the claimed combination of elements obvious, the Examiner must show that the results would have been predictable to one of ordinary skill in the art. See Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Section III(D), issued by the U.S. Patent and Trademark Office on October 10, 2007.

In regard to independent claims 38 and 57, Bennett in view of Park fails to disclose or render predictable at least the elements of “a topical pharmaceutical composition comprising at least one oligonucleotide having between 7 and 25 nucleotides, capable of specifically hybridising with genes or gene products coding for protein kinase C beta-1 (PKC beta-1) and modifying expression of only PKC beta-1” as recited in amended claims 38 and 57.

In the Action the Examiner alleges that independent claims 38 and 57 do not exclude the inhibition of PKC beta-2, since they use an open-ended “comprise” language, and that arguments concerning the fact that Park would prompt one of ordinary skill in the art to use oligonucleotides targeting both PKC beta-1 and PKC beta-2 are thus not persuasive.

Independent claims 38 and 57 have been amended in order to make it clear that other PKC isozymes, including PKC beta-2 are not inhibited by the claimed composition. In addition, Applicants respectfully submit herewith a Declaration Pursuant to 37 CFR §1.132 by inventor Robin Kurfurst attesting to the fact that inhibition of PKC beta-1 only is sufficient to inhibit melanogenesis and obtain depigmentation, and such result is unexpected in view of the cited prior art references.

Neither Bennett nor Park alone disclose a method of depigmenting or bleaching human skin, body hair or hair on a head of a subject using a topical composition capable of modifying expression of only PKC beta-1 as claimed in the instant Application.

Applicants respectfully submit that in order to find claims 38 and 57 obvious, the Examiner must identify prior art documents which would have motivated one of ordinary skill in the art to depigment the skin using a composition inhibiting only PKC beta-1 and not other PKC isozymes, including PKC beta-2.

In regard to the Examiner’s suggestion that Table 3 found on page 26 of Bennett provides motivation for one of ordinary skill in the art to use oligonucleotides targeting PKC beta-1 only, Applicants respectfully disagree.

While Bennett may suggest oligonucleotides targeting PKC beta-1 only, and thus suggests the use of a PKC beta-1 specific oligonucleotide if needed, it is important to highlight that Bennett may only provide motivation to use such oligonucleotides for the treatment of diseases associated to PKC beta-1 only.

Indeed, at multiple occurrences in the description, Bennett highlights the importance of specifically targeting PKC isozymes associated to the disease to be treated.

In particular, in page 3 lines 14-20, Bennett teaches:

*“PKC is not a single enzyme, but a family of enzymes. At the present time at least seven isoforms (isozymes) of PKC have been identified:  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -,  $e$ -,  $\zeta$  and  $\eta$ . These isozymes have distinct patterns of tissue and organ localization (see Nishizuka, *Nature*, 334:661-665 (1988) for review) and may serve different physiological functions.”*

Similarly, in page 5 lines 7-9, Bennett indicates:

*“There is also a desire to inhibit specific PKC isozymes, both as a research tool and as treatment for diseases which may be associated with particular isozymes.”*

The main teaching of Bennett is thus that, for the treatment of a particular disease, one of ordinary skill in the art should use oligonucleotides specific for one or more PKC isoforms that are known to be associated to this particular disease.

Bennett then provides one of ordinary skill in the art with oligonucleotides specific for all known PKC isozymes, including PKC beta. Tables 2 to 4 provide oligonucleotides specific for both PKC beta-1 and PKC beta-2 (Table 2), PKC beta-1 only (Table 3), and PKC beta-2 only (Table 4).

While Bennett does not disclose any disease associated to PKC beta-1 and PKC beta-2, PKC beta-1 only, or PKC beta-2 only, it is clear from the global teaching of Bennett that oligonucleotides of Table 2 should be used for diseases associated to both PKC beta-1 and PKC beta-2, oligonucleotides of Table 3 should be used for diseases associated to PKC beta-1 only, and oligonucleotides of Table 4 should be used for diseases associated to PKC beta-2 only. For diseases associated to both PKC beta-1 and PKC beta-2, a combination of an oligonucleotide of Table 2 with an oligonucleotide of Table 4 may be used alternatively.

In summary, the teachings of Bennett are that specific oligonucleotides should be used depending on the knowledge concerning which PKC isoform(s) is/are associated to a particular disease.

## 1. Teachings of Park and Nishizuka

As explained in the previous response and Declaration Pursuant to 37 CFR §1.132 attached herewith, Park, which only refers to PKC beta, without indicating which isoform of PKC beta has been tested, would have been interpreted by one of ordinary skill in the art, at the time the invention was made, as involving both PKC beta-1 and PKC beta-2 in melanogenesis.

This is further supported by the teachings of the document titled *The Molecular Heterogeneity of Protein Kinase C and Its Implications for Cellular Regulation* (1988) to Nishizuka (submitted in the IDS filed on February 5, 2008) (“Nishizukal”) see also, Declaration ¶¶ 15-18. This document is cited in Bennett in the above indicated paragraph of page 3 lines 14-20, and would thus clearly have been consulted by one of ordinary skill in the art.

Indeed, in the legend to Figure 1, Nishizukal indicates:

*“The  $\beta I$  and  $\beta II$  subspecies, which seem to be derived from a single messenger RNA by alternative splicing, differ from each other only in ~50 amino acid residues at their carboxy-terminal end regions,  $V_5$ , and even in this area they possess a high degree of sequence homology”*

In view of this statement, one of ordinary skill in the art would have concluded that PKC beta-1 and beta-2 isoforms most probably have about the same functions, and would thus have been incited, based on Park, to inhibit both isoforms for depigmentation applications.

Nishizuka further mentions, on page 663, second paragraph of the section entitled “*Individual characteristics*” that PKC beta-1 and PKC beta-2 subspecies have undistinguishable kinetic properties in response to stimulation by the same compound.

This would further have motivated one of ordinary skill in the art not to target PKC beta-1 only.

Nishizuka also indicate in page 662, right column, that PKC beta-2 is more expressed than PKC beta-1, at least in brain. Furthermore, Table 1 in page 662 indicates that PKC beta-2 is expressed in many tissues and cells, while PKC beta-1 is only expressed in some tissues and cells. This would also have deterred one of ordinary skill in the art to target PKC beta-1 only, since PKC beta-2 has higher probability to be expressed in large quantities in melanocytes.

In summary, the combined teachings of Park and Nishizuka would clearly have deterred one of ordinary skill in the art to target PKC beta-1 only for depigmentation purposes.

2. Results of the instant application are unexpected

Despite the fact that the prior art globally deterred one of ordinary skill in the art to target PKC beta-1 only for depigmentation purposes, the inventors of the instant Application found unexpectedly that the specific targeting of PKC beta-1 is sufficient to inhibit melanogenesis. See Declaration ¶¶7-9.

In particular, Applicants respectfully direct the Examiner's attention to the fact that only oligonucleotides targeting specifically PKC beta-1 are used in the experiments of Examples 2 to 4 of the instant application. The observed effect on melanogenesis is thus clearly and unambiguously linked to inhibition of PKC beta-1 only.

Since, for at least the foregoing reasons, the combination of Bennett and Park may not be relied upon to disclose each of the elements of claims 38 and 57, a *prima facie* case of obviousness may not be established. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 38 and 57 under 35 U.S.C. §103 in view of Bennett and Park.

Claims 42-56 and 60-67 depend from claim 1 and incorporate the limitation thereof. For at least the reasons that claim 1 is not *prima facie* obvious in view of Bennett and Park, claims 42-56 and 60-67 are further not obvious over the cited prior art references. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42-56 and 60-67 under 35 U.S.C. §103 in view of Bennett and Park.

## CONCLUSION

In view of the foregoing, it is believed that all claims now pending patentably define the subject invention over the prior art of record and are in condition for allowance and such action is earnestly solicited at the earliest possible date.

If necessary, the Commissioner is hereby authorized in this, concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17, particularly extension of time fees.

## PETITION FOR EXTENSION OF TIME

Per 37 C.F.R. 1.136(a) and in connection with the Office Action mailed on June 16, 2010, Applicants respectfully petition Commissioner for a three (3) month extension of time, extending the period for response to December 16, 2010. The amount of \$1,110.00 to cover the petition filing fee for a 37 C.F.R. 1.17(a)(3) large entity will be charged to our Deposit Account No. 02-2666.

Respectfully submitted,

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## CERTIFICATE OF TRANSMISSION

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12/14/10